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DOI: <https://doi.org/10.3109/15563650.2015.1022896>

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ZORA URL: <https://doi.org/10.5167/uzh-109867>

Journal Article

Accepted Version

Originally published at:

Martos, Viktor; Hofer, Katharina E; Rauber-Lüthy, Christine; Schenk-Jaeger, Katharina M; Kupferschmidt, Hugo; Ceschi, Alessandro (2015). Acute toxicity profile of tolperisone in overdose: Observational poison centre-based study. *Clinical Toxicology*, 53(5):470-476.

DOI: <https://doi.org/10.3109/15563650.2015.1022896>

Acute toxicity profile of tolperisone in overdose: observational poison centre-based study

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The paper is written in UK English.

Running head: Acute toxicity profile of tolperisone in overdose.

Word count (excluding references, figure, and abstract): 2075

References: 29

Figures: 3

Tables: 3

Keywords: Centrally acting muscle relaxant; Sodium channel blocker; Poisoning; Toxicity; Seizures.

Grant or other financial support: The present work was supported entirely by internal resources of the participating study sites.

ABSTRACT

Introduction: Tolperisone is a centrally-acting muscle relaxant that acts by blocking voltage-gated sodium and calcium channels. Information on the clinical features of tolperisone poisoning is lacking in the literature. The aim of this study was to investigate the demographics, circumstances, and clinical features of acute overdoses with tolperisone.

Methods: An observational study of acute overdoses with tolperisone in adults and children (<16 y), either alone or in combination with one non-steroidal anti-inflammatory drug in a dose range not expected to cause central nervous system effects, reported to our poison centre between 1995-2013.

Results: 75 cases were included: 51 females (68%) and 24 males (32%); 45 adults (60%) and 30 children (40%). Six adults (13%) and 17 children (57%) remained asymptomatic, and mild symptoms were seen in 25 adults (56%) and 10 children (33%). There were nine adults (20%) with moderate symptoms, and five adults (11%) and three children (10%) with severe symptoms. Signs and symptoms predominantly involved the central nervous system: somnolence, coma, seizures, and agitation. Furthermore, some severe cardiovascular and respiratory signs and symptoms were reported. The minimal dose for seizures and severe symptoms in adults was 1500 mg. In 11 cases the latency between the ingestion and the onset of symptoms was known and was reported to be 0.5 - 1.5 h.

Conclusions: The acute overdose of tolperisone may be life-threatening, with a rapid onset of severe neurological, respiratory, and cardiovascular symptoms. With alternative muscle relaxants available, indications for tolperisone should be rigorously evaluated.

INTRODUCTION

Tolperisone is a centrally acting muscle relaxant¹ with an additional vasodilating effect.² This piperidine derivative (1-piperidino-2-methyl-3-(p-tolyl)-propan-3-on) has been used for decades mainly in Europe and Asia for the treatment of muscle spasticity of neurological origin and muscle pain and muscle spasms due to rheumatologic conditions.¹ Tolperisone has also been proposed for the treatment of peripheral vascular disease.³

The precise mechanism of the muscle relaxing effect of tolperisone is not fully understood. It is supposed that tolperisone inhibits voltage-gated sodium and calcium channels mainly in the brainstem and at spinal cord level, resulting in membrane stabilization and leading to a reduced spinal mono- and polysynaptic reflex activity.⁴

In clinical studies tolperisone was well tolerated with minor side effects including nausea, headache, and dizziness.^{1,5} Nevertheless, anaphylactic reactions have been reported and the European Medicines Agency therefore recommended restricting the use of tolperisone for the treatment of adults with post-stroke spasticity.^{6,7} Although being a centrally acting muscle relaxant, a sedating effect was not observed in therapeutic dose.⁸ Despite being considered relatively safe in overdose,⁹ there is a forensic publication describing three fatalities due to tolperisone poisoning.¹⁰ Information on the clinical features of tolperisone poisoning is lacking in the literature. The aim of this study was to investigate the demographics, circumstances, and clinical features of acute overdoses with tolperisone using data reported to a single national poison centre during a 19-year period.

METHODS

National Poisons Centre operational procedures and data collection methods

Tox Info Suisse provides 24-hour 7-days-a-week nationwide free medical advice to healthcare professionals and the general public (referral population approximately 8 million) for the management of cases of human poisoning by any substance. Demographic and detailed clinical information on exposure cases such as age, weight, and sex of the patient, circumstances of the poisoning, ingested doses of all substances involved, symptoms and advice provided are recorded in a standardized

manner by clinical toxicologists who are blinded to any study hypotheses. The case records include all reported signs and symptoms. Data are anonymized and prospectively entered into an in-house database. Follow-up data including drug concentrations, therapeutic interventions and any decontamination measures which were performed and clinical course and complications are collected using standardized report forms sent to the treating physicians in the days after the initial contact. Before finalizing recording into the database, each case was reviewed by a senior clinical toxicologist to ensure completeness and correctness of the data.

Study design

We performed a retrospective review of all acute overdoses involving tolperisone in adults and children (<16 years), either alone or in combination with a non-steroidal anti-inflammatory drug (NSAID) in a dose not expected to cause central nervous system effects, that had been reported to our poisons centre between January 1995 and December 2013. All cases were reviewed in detail by the first authors before they were entered into the study to ensure that they fulfil the inclusion criteria. Doubts were resolved by consensus in an expert panel including a senior clinical toxicologist and a senior clinical pharmacologist with additional qualification in general internal medicine.

Assessment of symptom severity and causal relationship

The severity of symptoms was graded in accordance with the Poisoning Severity Score (PSS) - which has been developed by the European Association of Poison Centres and Clinical Toxicologists, the International Programme on Chemical Safety, and the European Commission - as 'minor', for mild, transient and spontaneously resolving symptoms/signs; 'moderate', if at least one pronounced or prolonged symptom/sign was recorded; 'severe', if at least one severe or life-threatening symptom/sign was observed, or 'fatal', if the overdose was the recorded cause of death.¹¹ Cases were assessed for association between symptoms and the tolperisone overdose, by an expert panel including a senior clinical toxicologist and a senior clinical pharmacologist with additional qualification in general internal medicine, using the World Health Organisation Uppsala Monitoring Centre (WHO-UMC) standardised case causality assessment criteria originally developed for the assessment of adverse drug reactions¹². Comorbidities and the magnitude of

overdose were taken into consideration (therapeutic tolperisone dose range in adults 150 mg three times daily; in children 5–10 mg/kg/day¹³). Associations were classified as `certain`, `likely`, `possible` and `unlikely`, and cases with certain or likely causal relationship were included. For the evaluation of the dose-effect relationship, the weight of the patient and the ingested tolperisone dose had to be known.

Data analysis

Descriptive statistics were used to analyze grouped data. Odds ratios (ORs) with 95% confidence intervals (CIs) and the Fisher exact probability test with two-tailed p-values were calculated using the software package VassarStats, Vassar College, Poughkeepsie, NY, USA (<http://vassarstats.net/>). Statistical significance was defined as $p < 0.05$.

Ethics approval

A specific ethics approval was not required for this observational study due to the nature of the study design according to the regulations of the cantonal ethics committee Zurich, Switzerland, which also stated that irreversibly anonymized data generated during patient care can be used retrospectively for research purposes without obtaining written consent.

RESULTS

A search of our database identified 652 cases related to tolperisone ingestion during the study period. The exclusion process is reported in Figure 1. A total of 75 cases fulfilling all inclusion criteria were available for analysis; of these, 72 were cases of single substance overdose and three were tolperisone overdoses with coingestion of one NSAID (one case with ibuprofen max. 6000 mg, one with ibuprofen 3600 mg, and another with acetaminophen 1200 mg). All were acute oral overdoses with film coated tablets (50 and 150 mg; no extended-release tablets). The number of acute tolperisone overdoses during the 19 years study period is shown in Figure 2.

The demographic characteristics of the patients were as follow: 51 females (68%) and 24 males (32%); 45 adults (60%, range 16 - 83 y) and 30 children (40%, range

1.1 - 15.9 y). Accidental ingestion occurred in all children younger than 12 y (n=22) and in three adults, whereas intentional overdose, mostly with suicidal attempt, in all other adults (n=42) and children older than 12 (n=8).

Six adults (13%) and 17 children (57%) remained asymptomatic, whereas mild symptoms were seen in 25 adults (56%) and 10 children (33%), respectively. There were nine adults (20%) with moderate symptoms, and five adults (11%) and three children (10%) with severe symptoms (Table 1). Among the three patients who coingested a NSAID, there were two severe cases (Table 3) and one asymptomatic case. There were no fatalities.

Signs and symptoms predominantly involved the central nervous system, with somnolence being the most frequently reported, followed by generalized tonic-clonic seizures, coma, and apnoea (Table 2). The main clinical characteristics of the severe cases are outlined in Table 3.

Especially noteworthy are two cases with a rapid onset of severe symptoms in toddlers:

1) a 21-months-old patient ingested up to 2700 mg (225 mg/kg) of tolperisone and 35 minutes later developed generalized tonic-clonic seizures, apnoea, and cardiac arrest at the doctor's office. Circulation was reestablished after prolonged resuscitation efforts, and the child showed severe acidosis (pH 6.98), hypokalemia (2.4 mmol/L), and signs of cerebral hypoxia with tetraspasticity. Plasma tolperisone concentration 14 h after the ingestion was 720 µg/L (therapeutic peak plasma concentrations in adults: 64 - 785 µg/L, T_{max} 0.9 h).¹⁴ After nine month of rehabilitation the patient had persistent neurological sequelae such as developmental impairments and muscle spasticity.

2) a 19-months-old patient ingested up to 1500 mg (150 mg/kg) of tolperisone, with subsequent vomiting and rapid deterioration of the level of consciousness. One hour after the ingestion, the patient presented at the emergency department in a comatose state (Glasgow Coma Scale score of 3), showed a respiratory acidosis (pH 6.90), and required intubation and mechanical ventilation. A few hours later, the patient was extubated and fully recovered.

41 adults (91%) ingested a precisely known dose. The dose range was 300-4500 mg in the asymptomatic group (n=5), 900-4500 mg in those with minor toxicity (n=22), 500-4500 mg in those showing moderate toxicity (n=9), and 1500-15000 mg in those with severe toxicity (n=5). The minimal tolperisone dose for seizures was 1500 mg, and the minimal dose for coma was 3700 mg in adults. There were 14 children (47%) who ingested a known dose: eight remained asymptomatic after ingestion of 6.3-36.0 mg/kg, and six showed mild symptoms after ingestion of 3.1-83.3 mg/kg. In the remaining 20 cases, information about ingested dose was not precise enough to allow for inclusion of these cases in the above analysis of dose-effect relationship.

In 11 of the 75 cases (4 mild, 4 moderate, 3 severe) the latency between the ingestion and the onset of symptoms was known and was reported to be 30 to 90 minutes (mean 55).

Early gastrointestinal decontamination was performed significantly more frequently in children (15 cases, 50%) than in adults (10, 22%) (OR 3.5; 95% CI, 1.28-9.54; p=0.02). It mainly consisted in oral administration of activated charcoal (n= 22) and rarely gastric lavage (n=2) or induced emesis (n=1).

DISCUSSION

This observational study of tolperisone overdoses reported to a single national poison centre illustrates that, although tolperisone is considered to be relatively safe without sedative effects at therapeutic dose levels,⁸ overdose can cause serious toxicity, including coma, generalized seizures, severe respiratory depression, and cardiac arrest. No clear dose-effect relationship was observed in this study, and this is possibly due to the uncertainty on the amounts actually ingested by patients, as is the case for most retrospective studies with poison centres data, and the large inter-individual difference in plasma tolperisone concentrations, which has been reported to vary between 64 and 785 µg/L after a therapeutic tolperisone dose of 150 mg, although the extrapolation to the overdose setting may be questionable.¹⁵ Seizures were frequently seen in our patients, and had a rapid onset within the first hour after the ingestion. No seizures occurred during the subsequent clinical course. The

remarkable potential of tolperisone to cause seizures in overdose was also described in another study from our centre, and was shown to be comparable with that of tramadol, mefenamic acid, citalopram, and venlafaxine.¹⁶

The observed cardiovascular symptoms were predominantly mild, although there was a case of relevant prolongation of the QTc-interval (500 ms), and this has not been previously reported in the literature. The product information reports a case of unspecified QT-interval prolongation, which was observed in combination with a supraventricular and ventricular arrhythmia after the ingestion of 750 mg of tolperisone in a 11-month-old child.⁹ Furthermore, in our study there was a case of cardiac arrest that occurred in a child, but, unfortunately, we have neither further information regarding its development, nor an electrocardiogram.

In this study there were no fatal outcomes, although there is a forensic report describing tolperisone-related out-of-hospital fatalities: three women, aged 14-41 y, were found dead after apparent suicidal drug ingestion, and had post-mortem blood tolperisone concentrations of 7-19 mg/L, without other causes for death.¹⁰

Activated charcoal and gastric lavage were used for gastrointestinal decontamination in a large proportion of our patients, but, unfortunately we are not in a position to draw conclusions about its efficacy due to small case numbers and uncontrolled settings without plasma concentration measurements. However, on the basis of the chemical properties of tolperisone, a good adsorption onto activated charcoal is to be expected. Tolperisone has a molecular weight of 281.8 Dalton, meaning that it is expected to be readily adsorbed into the 10–1000 Å-sized charcoal pores of current activated charcoal products.¹⁷ The fact that gastrointestinal decontamination was performed in children more frequently than in adults, as we already found in two other studies from our centre,^{18,19} possibly reflects the earlier presentation of children to emergency services and the difficulty medical staff have in obtaining an accurate account of the amount of drug ingested. In any case, due to the rapid onset of life-threatening neurological, respiratory, and cardiovascular symptoms in some cases, the prompt initiation of emergency measures, even in the out-of-hospital setting, seems even more important than gastrointestinal decontamination procedures.

Eperisone, a related compound to tolperisone with a close chemical structure (Figure 3) and comparable pharmacodynamic properties, seems to have a similar acute toxicity profile as tolperisone. Actually, there is a report of a 18-month-old girl who developed recurrent seizures, coma, apnoea, and ventricular tachycardia 30 minutes after the ingestion of 100 mg of eperisone (therapeutic dose for adults 150 mg/day).²⁰ Furthermore, similar signs and symptoms as those found in our study were described in a case series of 13 eperisone overdoses.²¹ There is a report of eperisone-related prolongation of the QT interval, as we also observed in our study,²² and one of torsade de pointes.²³ These observations suggest a possible class effect regarding the acute toxicity profile of tolperisone and related centrally acting muscle relaxants.

Tolperisone is structurally related to lidocaine (Figure 3) and both substances bind to voltage dependent sodium channels.²⁴ Accordingly, we demonstrated that the acute toxicity profile of tolperisone shares some similarities with that of local anaesthetic agents, in particular the rapid onset of severe neurotoxicity.^{25,26} The systemic toxicity of local anaesthetics has been shown to be related to the time needed to reach the maximal plasma concentration,²⁷ which is quite short for tolperisone ($T_{max} = 0.9 \pm 0.3$ h).¹⁴ Although severe cardiotoxicity was rarely seen in our study, there might be a risk for cardiac arrhythmias, which are a characteristic manifestation of local anaesthetic agent toxicity. As acidosis is known to increase local anaesthetic toxicity²⁸ it seems plausible that conditions such as seizures and respiratory depression, which are observed in tolperisone overdose and are associated with acidosis, will further exacerbate tolperisone toxicity.

The interpretation of our findings is limited by the retrospective nature of the study design²⁹. In addition, our strict inclusion criteria led to small case numbers. However, we are convinced that these restrictions were necessary to be able to interpret the findings properly, in particular because we were mostly not able to obtain plasma concentrations of tolperisone. A further limitation is due to the fact that we also included two severe and one moderate case with coingestion of a NSAID, a drug class which is frequently coadministered with tolperisone. However, in all cases the NSAID dose was low, and not in a range expected to influence the clinical course.

CONCLUSIONS

In conclusion, the acute overdose of tolperisone may be life-threatening, with a rapid onset of severe neurological, respiratory, and cardiovascular symptoms. With alternative muscle relaxants available, the current indications for tolperisone should be rigorously evaluated.

Acknowledgments

We thank Mrs. Rose-Marie Hauser-Panagl for secretarial assistance.

Declaration of interest

The authors declare that there are no conflicts of interest.

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